VOLUME 33 · NUMBER 33 · NOVEMBER 20 2015

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Polycythemia Vera: An Appraisal of the Biology and Management 10 Years After the Discovery of *JAK2 V617F*

Brady L. Stein, Stephen T. Oh, Dmitriy Berenzon, Gabriela S. Hobbs, Marina Kremyanskaya, Raajit K. Rampal, Camille N. Abboud, Kenneth Adler, Mark L. Heaney, Elias J. Jabbour, Rami S. Komrokji, Alison R. Moliterno, Ellen K. Ritchie, Lawrence Rice, John Mascarenhas, and Ronald Hoffman

Brady L. Stein, Northwestern Feinberg University School of Medicine, Chicago, IL; Stephen T. Oh and Camille Abboud, Washington University School of Medicine, St Louis, MO; Dmitriy Berenzon, Wake Forest University School of Medicine, Winston Salem, NC; Gabriela S. Hobbs, Massachusetts General Hospital, Boston, MA; Marina Kremyanskaya, John Mascarenhas, and Ronald Hoffman, Mount Sinai School of Medicine; Raajit K. Rampal, Memorial Sloan Kettering Cancer Center; Mark L. Heaney, Columbia University Medical Center; Ellen K. Ritchie, Cornell University School of Medicine, New York, NY; Kenneth Adler, Regional Cancer Care Associates, Morristown, NJ; Elias J. Jabbour, MD Anderson Cancer Center; Lawrence Rice, Cornell Houston Methodist Hospital, Houston, TX; Rami S. Komrokji, Moffitt Cancer Center, Tampa, FL; and Alison R. Moliterno, Johns Hopkins University School of Medicine, Baltimore, MD.

Published online ahead of print at www.jco.org on August 31, 2015.

B.L.S. and S.T.O. serve as co-first authors.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Ronald Hoffman, MD, Tisch Cancer Institute, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1079, New York, NY 10029, e-mail: ronald.hoffman@mssm.edu.

0732-183X/15/3333w-3953w/$20.00

DOI: 10.1200/JCO.2015.61.6474

ABSTRACT

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm that is associated with a substantial symptom burden, thrombohemorrhagic complications, and impaired survival. A decade after the seminal discovery of an activating mutation in the tyrosine kinase *JAK2* in nearly all patients with PV, new treatment options are finally beginning to emerge, necessitating a critical reappraisal of the underlying pathogenesis and therapeutic modalities available for PV. Herein, we comprehensively review clinical aspects of PV including diagnostic considerations, natural history, and risk factors for thrombosis. We summarize recent studies delineating the genetic basis of PV, including their implications for evolution to myelofibrosis and secondary acute myeloid leukemia. We assess the quality of evidence to support the use of currently available therapies, including aspirin, phlebotomy, hydroxyurea, and interferon. We analyze recent studies evaluating the safety and efficacy of JAK inhibitors, such as ruxolitinib, and evaluate their role in the context of other available therapies for PV. This review provides a framework for practicing hematologists and oncologists to make rational treatment decisions for patients with PV.

J Clin Oncol 33:3953-3960. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Polycythemia vera (PV) is a clonal hematologic malignancy characterized by a pronounced symptom burden, including fatigue, pruritus, and symptomatic splenomegaly, along with an increased risk of thrombosis and the potential for evolution to myelofibrosis (MF) and secondary acute myeloid leukemia (sAML). The history of PV was previously divided into three eras.[1] The first era was marked by its initial descriptions by Vaquez in 1892 and Osler in 1903, and the introduction of therapeutic phlebotomy (TP). The second era, beginning in 1939, was characterized by diagnostic advances, allowing for distinction of relative and absolute polycythemia through measurement of red cell mass. Importantly, this era witnessed the first application of radioactive phosphorous as a treatment for PV, and the subsequent report of acute myeloid leukemia (AML) in patients treated with [^{32}]P. The third era marked the efforts of the Polycythemia Vera Study Group (PVSG), spanning from 1967 to 1997, which led to the development of formal diagnostic criteria and raised awareness about the effect of TP, long-term consequences of certain cytoreductive therapies, and consequently, the introduction of hydroxyurea (HU).

In 1997, PV entered the molecular biology era,[1] and the discovery of the *JAK2 V617F* mutation in 2005[2] marked the start of the fourth era of PV. The discovery of *JAK2 V617F* improved understanding of PV pathogenesis, facilitated diagnostic capability, and led to the reclassification of PV as a myeloid neoplasm. This landmark finding not only reinvigorated research efforts into understanding the genetic basis of PV but also ushered in the development of novel therapeutics (Fig 1). To date, the defining features of each era are relevant in the current molecular era of PV. TP remains a cornerstone of management, with the target hematocrit level being validated only recently.[3] Distinction of PV from secondary causes of erythrocytosis remains paramount, especially in patients lacking a *JAK2* mutation. Associations between cytoreductive treatments and leukemia continue to polarize the field. Because 10 years have passed since the seminal discovery of *JAK2 V617F*, it is important to critically reappraise what is known about the pathogenesis and management of PV.

EPIDEMIOLOGY

The prevalence of PV is estimated to be 44 to 57 cases per 100,000 persons,[4] and approximately 148,000

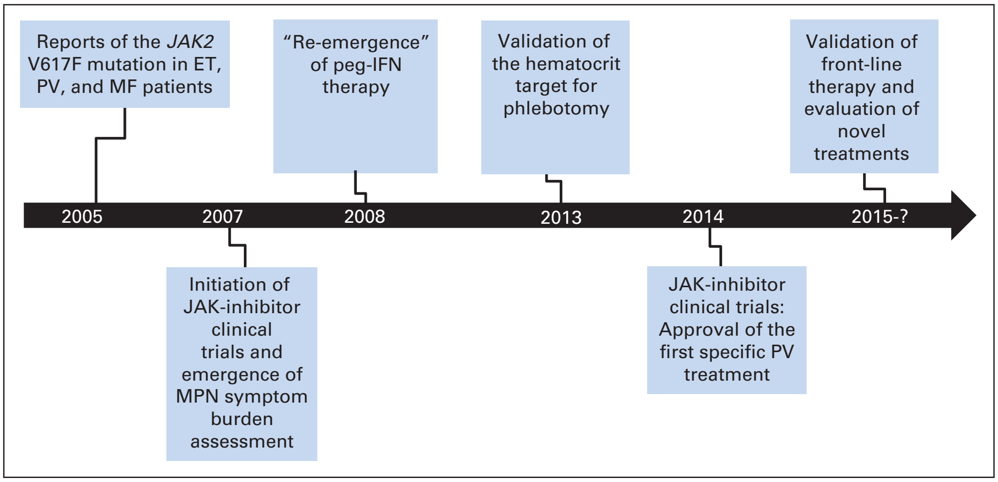

Fig 1. Polycythemia vera (PV): the *JAK2* discovery era, 2005 to present. ET, essential thrombocythemia; IFN, interferon; MF, myelofibrosis; MPN, myeloproliferative neoplasm; peg-IFN, pegylated IFN.

persons are living with PV in the United States. This may represent an underestimation, given that *JAK2 V617F* can be latent and PV asymptomatic, as evidenced by its detection in large, unselected population surveys.[5] These data indicate that PV is not rare, but rather, a relatively common hematologic malignancy. Although the median age at diagnosis is 61 years, PV has been diagnosed in all age groups.[6-8] PV was historically thought to occur more commonly in males, but females may account for 75% of patients younger than 40 years in whom PV is diagnosed.[6,8] Younger patients with PV appear to be at risk for unique complications, including abdominal venous thrombosis, and their disease appears to transform to MF and/or sAML as frequently as it does in older patients.[8]

DISEASE PATHOGENESIS: GENETIC UNDERPINNINGS OF PV

The genetic basis of PV was largely unknown until the discovery of an activating mutation, *V617F,* in the *JAK2* gene encoding tyrosine kinase in 2005.[2,9-11] The *V617F* mutation, located within the autoinhibitory pseudokinase domain of protein JAK2, leads to JAK2 kinase hyperactivity and aberrant cytokine-independent signaling through the JAK-STAT axis. It is now established that approximately 96% of patients with PV are positive for *JAK2 V617F.* In addition, about 2% to 3% harbor mutations in exon 12 of *JAK2,*[12,13] whereas rare patients with erythrocytosis and low erythropoietin (Epo) levels may carry mutations in LNK (SH2B3), a negative regulator of JAK-STAT signaling.[14] Clearly, activation of JAK2 and consequent downstream signaling is a hallmark of PV.

JAK2 V617F also occurs in approximately 50% of patients with essential thrombocythemia (ET) and PMF.[15] These findings indicate that *JAK2 V617F* is not specific to PV and raise the question of how a single mutation can result in such phenotypic diversity. *JAK2 V617F* mutant allele burden is typically highest in PV and lowest in ET, and *JAK2 V617F* homozygosity resulting from an acquired uniparental disomy is more common in PV than ET.[16-18] Patients with *JAK2 V617F*–positive ET tend to have higher hemoglobin (Hgb) levels and lower platelet counts than patients with *JAK2 V617F*–negative ET.[19,20] Therefore, higher levels of *JAK2 V617F* may create a more PV-like phenotype.

Although differences in *JAK2 V617F* allele burden appear to play an important role in differentiating myeloproliferative neoplasm (MPN) disease phenotypes, additional genetic factors likely contribute as well. Recent studies have revealed additional mutations in many patients with PV, although none are nearly as prevalent as *JAK2*, nor do any appear to be entirely specific to PV.[21,22] Mutations in *TET2* are present in a subset of MPNs, including PV, and they can occur either before (ie, pre-*JAK2*) or after the acquisition of *JAK2 V617F.*[23,24] Recent studies demonstrated that the order of acquisition of *TET2* versus *JAK2* mutations in MPNs may modulate disease phenotype.[25,26] Of note, patients in whom the *JAK2* mutation was acquired first were more likely to present with a diagnosis of PV than with ET.

Large-scale genomic studies have clarified the spectrum of genetic changes in PV.[21,22] Nangalia et al[21] performed exome sequencing on 151 patients with MPN including 48 with PV. The median number of mutations in PV was 6.5, which was approximately half that found in 39 patients with MF. These findings suggest that a relatively small number of pathogenic mutations are needed to initiate and establish PV. Although *CALR* mutations were identified in most patients with ET and MF lacking *JAK2 V617F, CALR* mutations have rarely been observed in PV.[27] *TET2* mutations were found in our (8.3%) of 48 patients in the PV cohort, whereas *SF3B1* and *DNMT3A* mutations were each identified in two patients. In a separate study of 31 patients with PV, exome sequencing revealed mutations in several additional genes, including *ASXL1.*[22] In MF, *ASXL1* mutations have been shown to be associated with worse overall survival and increased likelihood of transformation to sAML.[28] However, the implications of such mutations in PV are unclear. Several of these recurrently mutated genes play roles in epigenetic regulation (eg, *TET2*, *ASXL1, DNMT3A*) or RNA splicing (eg, *SF3B1*), and they are also mutated in other MPNs as well as myelodysplastic syndromes (MDS). Overall, these recently reported studies have highlighted the genetic complexity of PV, but the specific influence of individual mutations on PV disease phenotype remains incompletely understood.

DIAGNOSIS

The diagnosis of PV is currently based on the World Health Organization 2008 criteria, which include the presence of a *JAK2* mutation and increased red cell mass, in which sex-based Hgb values are used as a surrogate: greater than 16.5 g/dL in women and greater than 18.5 g/dL in men. Other criteria include consistent bone marrow histology, low Epo levels, and the formation of endogenous erythroid colonies (EEC).[29] Unfortunately, EEC testing is not routinely available and has been difficult to standardize. In addition, Epo levels are normal in 20% of cases and can also be suppressed in ET.[30] A proposed alternative system opposed using a Hgb threshold and instead suggested testing of nuclear red cell mass;[30] this was based on studies that upgraded ET to PV when this diagnostic test was used.[31-33] Reports describe decreased survival in patients with a masked PV presentation, that is, those with consistent features but Hgb levels below the World Health Organization threshold, as a result of a higher rate of transformation to MF and/or sAML compared with those with overt PV.[34] It is unclear if masked PV is an early form or distinct PV phenotype with a different prognosis.

New diagnostic criteria have been proposed that incorporate *JAK2* mutational testing, allowing for a lower Hgb threshold of 16 g/dL and 16.5 g/dL in women and men, respectively. The guidelines omit EEC testing, include characteristic bone-marrow histopathological abnormalities as a major criterion, and retain suppressed Epo levels.[35] Red cell mass and plasma volume studies, which are sensitive and specific determinants of blood volume not confounded by plasma volume expansion, are not available to most practitioners.

NATURAL HISTORY

Major complications of PV include its thrombotic tendency and its potential for later evolution to MF and/or sAML. More recently, a pronounced symptom burden, which often includes fatigue, pruritus, and symptoms from splenomegaly has been appreciated (Fig 2). This symptom burden negatively affects quality of life and is prominent, even in classically low-risk patients.[36]

Historically, thrombosis has been the most common consequence, leading to serious morbidity and implicated in as many as 37% of deaths.[37,38] The Gruppo Italiano Studio Policitemia followed 1,213 patients for as long as 33 years (mean, 6 years) and found thromboses in 41% of patients, including 20% with a thrombotic event as the presenting symptom. They found another 6% in the 2 years before diagnosis and 19% during follow-up.[37] Historically reported yearly thrombosis rates have been 2.5% to 4%. However, more recent studies show lower rates of thrombosis, perhaps because of more aggressive therapy.[3,7] Predominant is arterial thrombosis, particularly cerebrovascular accidents, whereas acute coronary syndromes have been the most common cause of death. Venous thrombosis is less common than arterial thrombosis, but it has been shown to adversely survival.[7] Hepatic vein thrombosis, or Budd-Chiari syndrome, and thromboses of the portal and/or mesenteric vein are also strongly associated with PV and are often a presenting feature. Microvascular symptoms, including headache, visual change, dizziness, and erythromelalgia, are also prominent and affect quality of life (Fig 2).

Traditional risk factors include advanced age and previous history of thrombosis (Table 1). Although the magnitude of risk is greater in older patients, younger patients are not protected. In a retrospective study of 120 patients with PV younger than 45 years at diagnosis, thrombosis rates were similar to those of patients with PV older than 65 years at diagnosis (27% *v* 31% [younger *v* older]).[8] However, the involved vascular bed differed, because venous events were more common in younger patients, especially women presenting with abdominal venous thrombosis (AVT). This observation suggests that young age and sex should be considered in the assessment of thrombosis risk.

Leukocytosis is an emerging but inconsistent risk factor for thrombosis (Table 1).[39-42] The degree of thrombocytosis has not been correlated with thrombotic risk.[49] Associations with *JAK2 V617F* allele burden have also been inconsistent. Some investigators reporting that increased thrombosis rates were associated with higher allele burden, whereas others found no association.[6,43-45] A high-risk gene expression profile has been associated with an increased thrombotic risk and other adverse outcomes despite similar leukocyte counts and *JAK2 V617F* allele burdens.[46]

Transformation to MF and/or sAML is a significant cause of mortality in PV and is likely largely related to disease duration

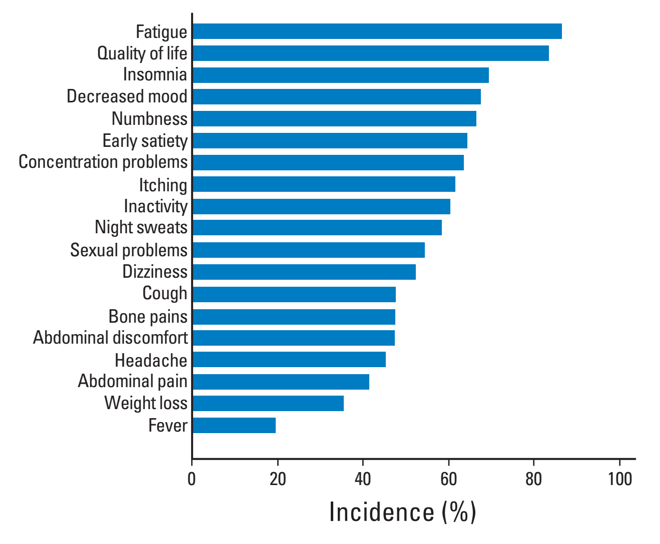

Fig 2. Patient-reported symptoms in polycythemia vera. Incidence of each symptom is estimated based on data from Scherber et al,[35a] Emmanuel et al,[35b] Johansson et al,[35c] and Abelsson et al.[35d]

Table 1. Risk Factors Associated With Increased Morbidity and Mortality in Patients With Polycythemia Vera

Risk Factors
For thrombosis
Age > 60 years
Previous history of thrombosis
Leukocytosis[39-42]*
Increased *JAK2 V617F* allele burden[6,43-45]*
High-risk gene expression profile[46]*
For transformation to myelofibrosis or secondary acute myeloid leukemia
Older age[47]
Longer disease duration[48]
Leukocytosis[41]
Exposure to phosphorus-32, pipobroman, or chlorambucil[7,48]
Risk factor associated with decreased survival
Older age[7]
Leukocytosis[7]
History of venous thrombosis[7]
Abnormal karyotype[7]

*Emerging or controversial risk factor.

(Table 1). In large studies, progression to MF was reported in 9% to 21% of patients with PV, while evolution to sAML has been documented in 3% to 10% of patients with PV.[7,48,50] Risk factors for transformation include older age and leukocytosis.[41,47] An increased risk of sAML has been associated with certain cytoreductive therapies.[7,48] The effect of the *JAK2 V617F* allele burden on disease evolution is not well established.[51] A potential role for mutations in other genes (eg, *ASXL1*) in modulating transformation risk is under investigation. Most prognostic systems developed for primary MF have excluded patients with post-PV MF. In an Italian study of 647 patients with PV, the median survival of 68 patients (10%) who developed MF was 5.7 years.[47] Multivariable analysis revealed three risk factors that adversely affected survival: WBC count greater than 30×10^9/L, Hgb concentration less than 10.0 g/dL, and platelet count less than 100×10^9/L. The prognosis for sAML after MPN, including PV, is dismal, with median survival of approximately 5 months.[52] Overall life expectancy for patients with PV is variable but significantly shorter than that of age-matched control subjects. A recent retrospective study demonstrated that survival varied from 10.9 to 27.8 years in high- and low-risk patients, respectively, and that it was most highly influenced by advanced age, leukocytosis, and history of venous thrombosis.[7]

THERAPEUTIC DECISION MAKING

Goals of Therapy

The primary goals of treatment are to reduce the risk for thrombosis, ameliorate the PV symptom burden, and prevent MF and/or sAML transformation. Unfortunately, current therapies are not effective for this latter purpose, and controlling blood counts may have less of an effect than anticipated. The European Leukemia Net (ELN) expert panel defined a complete response as a hematocrit less than 45% without phlebotomy, platelet count less than 400×10^9/L, leukocyte count less than 10×10^9/L, normal spleen size, and no disease-related symptoms.[53] However, in a study of 261 patients with PV who were given HU and followed up for a median of 4.4 years,[54] no association was observed between achieving an ELN or a hematocrit response and better survival or fewer vascular complications. No particular platelet or leukocyte count could be shown to be protective against thrombosis.[55] The ELN response criteria were updated in 2013, but they have not been validated to predict survival or progression to MF or AML.[56] In the subsequent sections, PV treatments are carefully reviewed.

ANTIPLATELET THERAPY

The routine use of aspirin for thromboprophylaxis is largely based on the European Collaboration on Low-dose Aspirin in Polycythemia Vera, or ECLAP, study in which 253 patients were randomly assigned to receive aspirin 100 mg per day and 265 patients, to receive placebo (Table 2). Total follow-up was 1,478 person-years.[57] Although the study did not meet its primary endpoint, which was cumulative rate of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, the observed trend was strongly in favor of aspirin therapy (relative risk [RR], 0.41; $P = .09$). The second primary endpoint was the cumulative rate of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes; it did achieve statistical significance (RR, 0.4; $P = .03$). A strong trend toward reducing the risk of major cerebrovascular events (RR, 0.32; $P = .08$) and major venous thrombotic events (RR, 0.49; 95% CI 0.24 to 0.74; $P = .003$) was observed. Evaluation of safety end points revealed no statistically significant difference in the incidence of major hemorrhages (RR, 1.62; $P = .6$).[57] To our knowledge, no published data describes the use of other antiplatelet agents, including clopidogrel.

PHLEBOTOMY

The notion that increased blood viscosity is a consequence of elevated hematocrit as the basis for hypercoagulability serves as the rationale

Table 2. Summary of Selected Clinical Trials Involving Patients With Polycythemia Vera

Study	No. of Subjects	Treatment	Results and Notes
PVSG 01	431	TP *v* phosphorus-32 plus TP *v* chlorambucil plus TP	Increased risk of thrombosis with TP alone but decreased risk of transformation to myelofibrosis or secondary acute myeloid leukemia and better overall survival; note initial HCT goal was < 50% and subsequently adjusted to < 45%
CYTO-PV	365	Low HCT, goal < 45% *v* high HCT, goal 45% to 50%	Lower HCT target associated with significantly lower rate of cardiovascular death and major thrombosis
ECLAP	518	Aspirin 100 mg per day *v* placebo	Aspirin significantly lowered the combined risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes; no significant difference in incidence of major hemorrhage
French PEG-IFN-α2a	37	PEG-IFN-α2a	95% CR at 12-month median follow-up *JAK2 V617F* allele burden decreased from median of 45% to 3% after 36 mo; molecular CR in 30% after 4 years
MDACC PEG-IFN-α2a	43	PEG-IFN-α2a	76% CR and 18% CMR at 42-month median follow-up; failure to achieve CMR was associated with mutations other than *JAK2 V617F*
RESPONSE	222	Ruxolitinib *v* BAT	Primary endpoint, a composite of phlebotomy independence and spleen volume reduction, was achieved in 21% of the ruxolitinib group *v* 1% of the BAT group; symptom improvement of > 50% occurred in 49% of the ruxolitinib group *v* 5% of the BAT group

Abbreviations: BAT, best available therapy; CR, complete response; CMR, complete molecular response; CYTO-PV, Cytoreductive Therapy in Polycythemia Vera; ECLAP, European Collaboration on Low-Dose Aspirin in Polycythemia Vera; HCT, hematocrit; MDACC, MD Anderson Cancer Center; PEG-IFN, pegylated interferon; PSVG, Polycythemia Vera Study Group; RESPONSE, randomized, open label, multicenter phase III study of efficacy and safety in polycythemia vera subjects who are resistant to or intolerant of hydroxyurea: JAK inhibitor INC424 tablets versus best available care; TP, therapeutic phlebotomy.

for phlebotomy, which remains an essential component of modern PV therapy.[58] Recently, after decades of debate, a hematocrit target of 45% or less was associated with a lower risk of cardiovascular morbidity and mortality than that associated with a goal hematocrit of 45% to 50% (Table 2).[3] Of note, patients in the lower hematocrit arm may have had more aggressive HU use and a lower leukocyte count, factors that may modify the effect of TP.

However, historical studies raised concerns about TP. In the PVSG 01 study, 431 patients with PV were randomly assigned to receive TP alone, [^{32}]P plus TP, or chlorambucil plus TP (Table 2).[59] Thrombosis-free cumulative survival was worse in the TP-alone arm. The need for more than four therapeutic phlebotomies a year in the TP-alone arm was associated with increased thrombotic risk. This led to the belief that frequent TP requirements were detrimental and necessitated cytoreductive therapy. However, overall survival and risk of evolution to MF and sAML were lower in the TP alone arm. Certain concerns about TP may be unfounded. Iron deficiency is a consequence of repeated TP; but, in fact, it should be viewed as a therapeutic goal to further limit erythropoiesis. Although iron deficiency can be associated with a number of clinical signs and symptoms, including glossitis, dysphagia, cheilosis, koilonychia, fatigue, global weakness, cognitive deficits, neuromuscular disturbances, and pica syndrome, these rarely prompt treatment discontinuation.[60]

CYTOREDUCTIVE THERAPY: BALANCING RISKS AND BENEFITS

Cytoreduction is typically prescribed for high-risk patients, that is, those with advanced age and/or thrombosis history. Uncontrolled disease-related symptoms, including those due to splenomegaly; intolerance of phlebotomy; extreme thrombocytosis; and progressive leukocytosis may also prompt therapy.[61] HU is considered a first-line cytoreductive therapy in PV, but evidence to support its efficacy in preventing thrombosis is typically extrapolated from studies of ET.[62,63] Its use in PV is based on a perceived balance of safety and efficacy rather than data from randomized studies showing thrombosis reduction. Rates of thrombosis appeared to be lower than those of historical control subjects treated with TP alone (9.8% *v* 32.8%), and lower rates of sAML (5.9%) were noted for HU compared with chlorambucil (17%) and [^{32}]P (10%) from the PVSG 01 and PVSG 08 protocols.[64] The rate of sAML in historical control subjects treated with TP was 1.5%, but this was not statistically different from the rate in patients treated with HU.

Data from large studies have not implicated single-agent HU as a cause of AML.[38,65] In a recent retrospective, multicenter study of 1,545 patients with PV, HU was implicated only when it was used in combination with pipobroman.[7] In a population-based study, researchers utilized the Swedish MPN registry of 11,039 patients to compare 162 patients with MPN (110 with PV) and AML and/or MDS transformation to 242 matched control subjects (176 with PV). They found no association between any cumulative dose of HU and transformation.[66] In a randomized study, the French Polycythemia Study Group compared HU and pipobroman. Higher rates of AML/MDS and shortened survival were observed in patients treated with pipobroman during long-term follow-up over 16 years.[67] Rates of AML and/or MDS in the HU arm at 10, 15, and 20 years were higher than expected at 6.6%, 16.5%, and 24.2%, respectively. However, this may reflect the natural history of PV with long follow-up.

The controversial association between HU and AML will be difficult to resolve with certainty, given inherent challenges to the conduct of a definitive clinical trial. Intrinsic as well as therapy-related contributions likely exist.[68] The risk of leukemia with cytoreductive therapies cannot be evaluated by absolute terms but by the magnitude of risk,[68] which appears to be lower with HU than with other agents such as chlorambucil, busulfan, [^{32}]P, and pipobroman.[7,65,66,69,70] These latter treatments may still have a role in the treatment of elderly patients with PV or those with medical comorbidities that are likely to substantially shorten survival in their own right.[71,72] Careful patient selection, improved sophistication in assessing vascular risk, and establishment of evidence-based or consensus-driven guidelines for rational use of cytoreductive agents, including HU, are needed.

EMERGING TREATMENTS

Interferon Therapy

Renewed enthusiasm for use of pegylated interferon (PEG-IFN), an agent without known leukemogenic effects, originated from the French phase II study of PEG-IFN-α-2a (PEG-IFN-α-2a) in patients with newly diagnosed PV (Table 2).[73] PEG-IFN-α-2a was started at 90 μg weekly for 2 weeks, with a dosage escalation in the absence of hematologic response. At 12 months, 95% of patients achieved a complete hematologic response (CHR). Only three patients (8%) had stopped treatment. Sequential monitoring of *JAK2 V617F* allele burden in 29 patients showed a decrease in 26 (90%), with a median decrease from 45% to 22%, 5%, and 3% after 12, 24, and 36 months, respectively. Complete molecular response (CMR), that is, undetectable *JAK2 V617F,* was achieved in seven patients. CMR lasted from at least 6 to at least 18 months and persisted after discontinuation in five patients. It should be noted that the clinical relevance of allele burden reduction is not yet clear. No vascular events were recorded.[73] In a recent update, the cumulative incidence of CMR was 14% and 30% of patients at 2 and 4 years, respectively.[74] Moreover, 27% of patients treated maintained CHR after PEG-IFN-α-2a was discontinued.

Another group evaluated PEG-IFN at the dosage of 90 μg weekly in 43 patients with newly diagnosed and previously treated disease (Table 2).[75] After a median follow-up of 42 months, CHR was achieved in 76% of patients with a median time of 40 days; CMR was reported in 18% of patients. No patient who achieved CMR had a relapse during the course of treatment with PEG-IFN-α-2a. No grade 4 toxicities occurred, and grade 3 adverse effects were infrequent. To date, 32% of patients have been removed from the study. In 18% of patients, treatment discontinuation was directly related to PEG-IFN-α-2a. Two patients remained in CHR and CMR 4 and 18 months after treatment discontinuation. Patients who did not achieve CMR had a higher frequency of mutations outside the JAK-STAT pathway and were more likely than others to acquire new mutations during therapy. Patients with both *JAK2 V617F* and *TET2* mutations at the onset of therapy had a higher *JAK2* V617F allele burden and a less significant reduction in *JAK2 V617F* allele burden than those of patients with a *JAK2* mutation and wild-type*TET2*.[75]

Although this is considered first line,[61] high-quality evidence supporting this recommendation is not yet available. Rather, randomized trials of PEG-IFN-α-2a versus HU in patients with newly diagnosed PV as well as those with HU intolerance/resistance or previous AVT are ongoing (ClinicalTrials.gov identifiers:

NCT01259856 and NCT01259817). The completion of such trials is necessary to enable an objective evaluation of the long-term tolerability, safety, and therapeutic value of PEG-IFN therapy for patients with PV, including the potential to reduce thrombotic risk or evolution to MF and/or sAML.

JAK1/2-INHIBITION THERAPY

In a phase II clinical trial, of 34 patients with PV treated with the JAK1/2 inhibitor ruxolitinib, 97% achieved a clinicohematologic response, with a complete response achieved by 59% according to modified 2009 ELN criteria.[76] Durable hematocrit control, reduction in leukocyte and platelet counts, and a reduction in palpable splenomegaly of 50% or greater by week 24 were observed, along with improvement in the PV symptom burden. Within 4 weeks of treatment, most experienced reduction of 50% or greater in the severity of pruritus, night sweats, and bone pain. After 3 years of ruxolitinib, nearly one quarter of patients achieved a 50% or greater reduction in the *JAK2 V617F* allele burden.[76]

A randomized, open-label, phase III clinical trial of ruxolitinib versus best available therapy (BAT) was subsequently conducted in patients with PV with splenomegaly, HU resistance or intolerance, and an ongoing requirement for phlebotomy (Table 2).[77] The primary endpoint was the composite of independence from phlebotomy and reduction in splenic volume. Overall, 222 patients were randomly assigned to receive ruxolitinib or BAT, which most commonly included HU despite the fact that HU intolerance or resistance was an entry criterion. The combined primary endpoint was achieved by 21% versus 1% of patients ($P < .001$) randomly assigned to receive ruxolitinib versus BAT, respectively. At week 48, 91% of patients maintained their response. Treatment with ruxolitinib was associated with greater benefit for both hematocrit control without phlebotomy (ruxolitinib, 60%; BAT, 20%), and splenic volume reduction (ruxolitinib, 38%; BAT, 1%). Symptom burden, as assessed by using the MPN symptom-assessment form, improved by greater than 50% in 49% versus 5% of patients randomly selected to be given ruxolitinib versus BAT. Among patients receiving ruxolitinib, grade 3 or greater adverse events included anemia in 1.8% and thrombocytopenia in 5.5%. These results led to the approval of ruxolitinib in December 2014 by the US Food and Drug Administration for use in patients with PV and HU resistance or intolerance.

Because of the study design, the investigators could not address the effect of ruxolitinib therapy on the incidence of thromboembolic events or disease progression.[77] Important issues that may influence use beyond the treatment of patients with HU resistance or intolerance are a lack of information about long-term safety, with a potentially increased risk of herpes simplex virus noted; the high cost; and whether the natural history can be altered by JAK 1/2-inhibition in PV. Therefore, this agent is currently considered a second-line therapy.

CONCLUSION

Despite important breakthroughs in our understanding of PV, several important concepts require further insight. Although the discovery of *JAK2 V617F* represented a major breakthrough, our understanding of the genetic basis for PV remains incomplete; likely contributing factors include additional host modifiers and additional somatic mutations. PV diagnostic criteria continue to evolve, with consideration of the appropriate Hgb threshold. Thrombosis risk assessment remains generic rather than personalized, and the ongoing challenge is to identify surrogate markers that can enable individualized assessment of thrombosis risk. The same challenge exists in identifying early on those with a potential for aggressive disease, yet additional prognostic indicators, apart from disease duration, *JAK2* allele burden, and leukocytosis are needed. With regard to therapeutic goals, meeting response criteria has less of an impact than anticipated; further, the natural history of PV creates inherent limitations to trial design that make it difficult to discern both long-term toxicity and efficacy. Although HU is considered a front-line cytoreductive therapy, its use is based more on historical, nonrandomized data, ease of administration, and opinion.[78] Similarly, PEG-IFN is intriguing, but has also been prematurely adopted as a front-line agent before the scrutiny of a randomized, phase III clinical trial.[78]

With regard to second-line therapy, patients with HU resistance or intolerance now have JAK inhibition as an approved option. Lack of information about long-term safety, high cost, and whether the natural history can be altered by JAK 1/2-inhibition in PV are important questions that may affect use beyond the patient population that is HU resistant or intolerant. Despite expanding treatment options, a need remains for new therapeutic interventions in PV, and many novel strategies can be seen as a potential complement to JAK inhibition, including HSP90 inhibition, targeting of other activated pathways (eg, PI3K, ERK, AKT/mTOR) or targeting epigenetic modifiers such as histone deactyleases.[79] Finally, preclinical data has demonstrated that an MDM2 inhibitor combined with PEG-IFN-α-2a can synergistically increase apoptosis and reduce *JAK2 V617F* allele burden in xenograft models.[80] Such a clinical trial is now underway (No. NCT02407080). Hopefully, the therapeutic potential of emerging treatments will be realized, and the next era will be characterized by significant alteration in the natural history of PV.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Brady L. Stein, Stephen T. Oh, Alison R. Moliterno, John Mascarenhas, Ronald Hoffman
Collection and assembly of data: Brady L. Stein, Stephen T. Oh, Dmitriy Berenzon, Gabriela S. Hobbs, Marina Kremyanskaya, Raajit K. Rampal, Camille N. Abboud, Mark Heaney, Elias J. Jabbour, Rami Komrokji, Alison R. Moliterno, Ellen K. Ritchie, Lawrence Rice, John Mascarenhas, Ronald Hoffman
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Berlin NI: Prologue: Polycythemia vera—The closing of the Wasserman-Polycythemia Vera Study Group era. Semin Hematol 34:1-5, 1997

2. James C, Ugo V, Le Couedic JP, et al: A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature 434: 1144-1148, 2005

3. Marchioli R, Finazzi G, Specchia G, et al: Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med 368:22-33, 2013

4. Mehta J, Wang H, Iqbal SU, et al: Epidemiology of myeloproliferative neoplasms in the United States. Leuk Lymphoma 55:595-600, 2014

5. Nielsen C, Birgens HS, Nordestgaard BG, et al: Diagnostic value of JAK2 V617F somatic mutation for myeloproliferative cancer in 49 488 individuals from the general population. Br J Haematol 160:70-79, 2013

6. Passamonti F, Rumi E, Pietra D, et al: A prospective study of 338 patients with polycythemia vera: The impact of JAK2 (V617F) allele burden and leukocytosis on fibrotic or leukemic disease transformation and vascular complications. Leukemia 24: 1574-1579, 2010

7. Tefferi A, Rumi E, Finazzi G, et al: Survival and prognosis among 1545 patients with contemporary polycythemia vera: An international study. Leukemia 27:1874-1881, 2013

8. Stein BL, Saraf S, Sobol U, et al: Age-related differences in disease characteristics and clinical outcomes in polycythemia vera. Leuk Lymphoma 54:1989-1995, 2013

9. Baxter EJ, Scott LM, Campbell PJ, et al: Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet 365: 1054-1061, 2005

10. Kralovics R, Passamonti F, Buser AS, et al: A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 352:1779-1790, 2005

11. Levine R, Wadleigh M, Cools J, et al: Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell 7:387-397, 2005

12. Pardanani A, Lasho T, Finke C, et al: Prevalence and clinicopathologic correlates of JAK2 exon 12 mutations in JAK2V617F-negative polycythemia vera. Leukemia 21:1960-1963, 2007

13. Scott LM, Tong W, Levine R, et al: JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. N Engl J Med 356:459-468, 2007

14. Lasho TL, Pardanani A, Tefferi A: LNK mutations in JAK2 mutation-negative erythrocytosis. N Engl J Med 363:1189-1190, 2010

15. Oh ST, Gotlib J: JAK2 V617F and beyond: Role of genetics and aberrant signaling in the pathogenesis of myeloproliferative neoplasms. Expert Rev Hematol 3:323-337, 2010

16. Scott LM, Scott MA, Campbell PJ, et al: Progenitors homozygous for the V617F mutation occur in most patients with polycythemia vera, but not essential thrombocythemia. Blood 108:2435-2437, 2006

17. Godfrey AL, Chen E, Pagano F, et al: JAK2V617F homozygosity arises commonly and recurrently in PV and ET, but PV is characterized by expansion of a dominant homozygous subclone. Blood 120:2704-2707, 2012

18. Godfrey AL, Chen E, Pagano F, et al: Clonal analyses reveal associations of JAK2V617F homozygosity with hematologic features, age and gender in polycythemia vera and essential thrombocythemia. Haematologica 98:718-721, 2013

19. Antonioli E, Guglielmelli P, Poli G, et al: Influence of JAK2V617F allele burden on phenotype in essential thrombocythemia. Haematologica 93:41-48, 2008

20. Kittur J, Knudson R, Lasho T, et al: Clinical correlates ofJAK2V617F allele burden in essential thrombocythemia. Cancer 109:2279-2284, 2007

21. Nangalia J, Massie CE, Baxter EJ, et al: Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med 369: 2391-2405, 2013

22. Wang L, Swierczek SI, Drummond J, et al: Whole-exome sequencing of polycythemia vera revealed novel driver genes and somatic mutation shared by T cells and granulocytes. Leukemia 28: 935-938, 2014

23. Delhommeau F, Dupont S, Della Valle V, et al: Mutation in TET2 in myeloid cancers. N Engl J Med 360:2289-2301, 2009

24. Tefferi A, Pardanani A, Lim KH, et al: TET2 mutations and their clinical correlates in polycythemia vera, essential thrombocythemia and myelofibrosis. Leukemia 23:905-911, 2009

25. Kent DG, Ortmann C, Silber Y, et al: Order matters: Sequence of mutation acquisition in myeloproliferative neoplasms impacts disease pathogenesis and stem cell potency. Blood 122:2888, 2013

26. Ortmann CA, Kent DG, Nangalia J, et al: Effect of mutation order on myeloproliferative neoplasms. N Engl J Med 372:601-612, 2015

27. Broseus J, Park JH, Carillo S, et al: Presence of calreticulin mutations in JAK2-negative polycythemia vera. Blood 124:3964-3966, 2014

28. Vannucchi AM, Lasho TL, Guglielmelli P, et al: Mutations and prognosis in primary myelofibrosis. Leukemia 27:1861-1869, 2013

29. Tefferi A, Thiele J, Orazi A, et al: Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: Recommendations from an ad hoc international expert panel. Blood 110:1092-1097, 2007

30. Spivak JL, Silver RT: The revised World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytosis, and primary myelofibrosis: An alternative proposal. Blood 112:231-239, 2008

31. Cassinat B, Laguillier C, Gardin C, et al: Classification of myeloproliferative disorders in the JAK2 era: Is there a role for red cell mass? Leukemia 22:452-453, 2008

32. Alvarez-Larran A, Ancochea A, Angona A, et al: Red cell mass measurement in patients with clinically suspected diagnosis of polycythemia vera or essential thrombocythemia. Haematologica 97: 1704-1707, 2012

33. Silver RT, Chow W, Orazi A, et al: Evaluation of WHO criteria for diagnosis of polycythemia vera: A prospective analysis. Blood 122:1881-1886, 2013

34. Barbui T, Thiele J, Gisslinger H, et al: Masked polycythemia vera (mPV): Results of an international study. Am J Hematol 89:52-54, 2014

35. Tefferi A, Thiele J, Vannucchi AM, et al: An overview on CALR and CSF3R mutations and a proposal for revision of WHO diagnostic criteria for myeloproliferative neoplasms. Leukemia 28:1407-1413, 2014

35a. Scherber R, Dueck AC, Johansson P, et al: The Myeloproliferative Neoplams Symptom Assessment Form (MPN-SAF): International Prospective Validation and Reliability Trial in 402 patients. Blood 118:401–440, 2011

35b. Emanuel RM, Dueck AC, Geyer HL, et al: Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 30:4098–4103, 2012

35c. Johansson P, Mesa R, Scherber R, et al: Association between quality of life and clinical parameters in patients with myeloproliferative neoplasms. Leuk Lymphoma 53:441–444, 2012

35d. Abelsson J, Andreasson B, Samuelsson J, et al: Patients with polycythemia vera have worst impairment of quality of life among patients with newly diagnosed myeloproliferative neoplasms. Leuk Lymphoma 54:2226–2230, 2013

36. Geyer HL, Scherber RM, Dueck AC, et al: Distinct clustering of symptomatic burden among myeloproliferative neoplasm patients: Retrospective assessment in 1470 patients. Blood 123:3803-3810, 2014

37. Polycythemia vera: The natural history of 1213 patients followed for 20 years: Gruppo Italiano Studio Policitemia. Ann Intern Med 123:656-664, 1995

38. Passamonti F, Rumi E, Pungolino E, et al: Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. Am J Med 117:755-761, 2004

39. Landolfi R, Di Gennaro L, Barbui T, et al: Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood 109:2446-2452, 2007

40. Barbui T, Carobbio A, Rambaldi A, et al: Perspectives on thrombosis in essential thrombocythemia and polycythemia vera: Is leukocytosis a causative factor? Blood 114:759-763, 2009

41. Gangat N, Strand J, Li CY, et al: Leucocytosis in polycythaemia vera predicts both inferior survival and leukaemic transformation. Br J Haematol 138: 354-358, 2007

42. De Stefano V, Za T, Rossi E, et al: Leukocytosis is a risk factor for recurrent arterial thrombosis in young patients with polycythemia vera and essential thrombocythemia. Am J Hematol 85:97-100, 2010

43. Carobbio A, Finazzi G, Antonioli E, et al: JAK2V617F allele burden and thrombosis: A direct comparison in essential thrombocythemia and polycythemia vera. Exp Hematol 37:1016-1021, 2009

44. Vannucchi AM, Antonioli E, Guglielmelli P, et al: Prospective identification of high-risk polycythemia vera patients based on JAK2(V617F) allele burden. Leukemia 21:1952-1959, 2007

45. Vannucchi AM, Antonioli E, Guglielmelli P, et al: Clinical profile of homozygous JAK2 617V>F mutation in patients with polycythemia vera or essential thrombocythemia. Blood 110:840-846, 2007

46. Spivak JL, Considine M, Williams DM, et al: Two clinical phenotypes in polycythemia vera. N Engl J Med 371:808-817, 2014

47. Passamonti F, Rumi E, Caramella M, et al: A dynamic prognostic model to predict survival in post-polycythemia vera myelofibrosis. Blood 111: 3383-3387, 2008

48. Marchioli R, Finazzi G, Landolfi R, et al: Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol 23:2224-2232, 2005

49. Di Nisio M, Barbui T, Di Gennaro L, et al: The haematocrit and platelet target in polycythemia vera. Br J Haematol 136:249-259, 2007

50. Tefferi A, Guglielmelli P, Larson DR, et al: Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. Blood 124: 2507-2513; quiz 2615, 2014

51. Koren-Michowitz M, Landman J, Cohen Y, et al: JAK2V617F allele burden is associated with transformation to myelofibrosis. Leuk Lymphoma 53:2210-2213, 2012

52. Tam CS, Nussenzveig RM, Popat U, et al: The natural history and treatment outcome of blast phase BCR-ABL-myeloproliferative neoplasms. Blood 112:1628-1637, 2008

53. Barosi G, Birgegard G, Finazzi G, et al: Response criteria for essential thrombocythemia and polycythemia vera: Result of a European LeukemiaNet consensus conference. Blood 113:4829-4833, 2009

54. Alvarez-Larran A, Pereira A, Cervantes F, et al: Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. Blood 119:1363-1369, 2012

55. Hernandez-Boluda JC, Gomez M: Target hematologic values in the management of essential thrombocythemia and polycythemia vera. Eur J Haematol 94:4-11, 2015

56. Barosi G, Mesa R, Finazzi G, et al: Revised response criteria for polycythemia vera and essential thrombocythemia: An ELN and IWG-MRT consensus project. Blood 121:4778-4781, 2013

57. Landolfi R, Marchioli R, Kutti J, et al: Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med 350:114-124, 2004

58. Kuriyama S: The expressiveness of the body and the divergence of Greek and Chinese medicine. New York, Zone Books, 1999

59. Berk PD, Goldberg JD, Donovan PB, et al: Therapeutic recommendations in polycythemia-vera based on polycythemia-vera study-group protocols. Semin Hematol 23:132-143, 1986

60. Rector WG, Fortuin NJ, Conley CL: Nonhematologic effects of chronic iron-deficiency: a study of patients with polycythemia-vera treated solely with venesections. Medicine 61:382-389, 1982

61. Barbui T, Barosi G, Birgegard G, et al: Philadelphia-negative classical myeloproliferative neoplasms: Critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol 29:761-770, 2011

62. Cortelazzo S, Finazzi G, Ruggeri M, et al: Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med 332:1132-1136, 1995

63. Harrison CN, Campbell PJ, Buck G, et al: Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med 353:33-45, 2005

64. Fruchtman SM, Mack K, Kaplan ME, et al: From efficacy to safety: A Polycythemia Vera Study group report on hydroxyurea in patients with polycythemia vera. Semin Hematol 34:17-23, 1997

65. Finazzi G, Caruso V, Marchioli R, et al: Acute leukemia in polycythemia vera: An analysis of 1,638 patients enrolled in a prospective observational study. Blood 105:2664-2670, 2005

66. Bjorkholm M, Derolf AR, Hultcrantz M, et al: Treatment-related risk factors for transformation to acute myeloid leukemia and myelodysplastic syndromes in myeloproliferative neoplasms. J Clin Oncol 29:2410-2415, 2011

67. Kiladjian JJ, Chevret S, Dosquet C, et al: Treatment of polycythemia vera with hydroxyurea and pipobroman: Final results of a randomized trial initiated in 1980. J Clin Oncol 29:3907-3913, 2011

68. Bjorkholm M, Hultcrantz M, Derolf AR: Leukemic transformation in myeloproliferative neoplasms: Therapy-related or unrelated? Best Pract Res Clin Haematol 27:141-153, 2014

69. Ledlie EM: Treatment of polycythaemia by 32-P. Proc R Soc Med 59:1095-1100, 1966

70. Berk PD, Goldberg JD, Silverstein MN, et al: Increased incidence of acute leukemia in polycythemia vera associated with chlorambucil therapy. N Engl J Med 304:441-447, 1981

71. Pearson TC, Messinezy M, Westwood N, et al: A polycythemia vera updated: Diagnosis, pathobiology, and treatment. Hematology Am Soc Hematol Educ Program 1:51-68, 2000

72. Barbui T, Finazzi MC, Finazzi G: Front-line therapy in polycythemia vera and essential thrombocythemia. Blood Rev 26:205-211, 2012

73. Kiladjian JJ, Cassinat B, Chevret S, et al: Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood 112:3065-3072, 2008

74. Turlure PC, Cambier N, Roussel M, et al: Complete hematological, molecular and histological remissions without cytoreductive treatment lasting after pegylated-interferon α-2a (peg-IFNα-2a) therapy in polycythemia vera (PV): Long term results of a phase 2 trial. Blood 118, 2011 (abstr 280)

75. Quintas-Cardama A, Abdel-Wahab O, Manshouri T, et al: Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon alpha-2a. Blood 122: 893-901, 2013

76. Verstovsek S, Passamonti F, Rambaldi A, et al: A phase 2 study of ruxolitinib, an oral JAK1 and JAK2 Inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea. Cancer 120:513-520, 2014

77. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al: Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med 372:426-435, 2015

78. Mascarenhas J, Mesa R, Prchal J, et al: Optimal therapy for polycythemia vera and essential thrombocythemia can only be determined by the completion of randomized clinical trials. Haematologica 99:945-949, 2014

79. Finazzi G, Vannucchi AM, Martinelli V, et al: A phase II study of Givinostat in combination with hydroxycarbamide in patients with polycythaemia vera unresponsive to hydroxycarbamide monotherapy. Br J Haematol 161:688-694, 2013

80. Lu M, Xia L, Li Y, et al: The orally bioavailable MDM2 antagonist RG7112 and pegylated interferon alpha 2a target JAK2V617F-positive progenitor and stem cells. Blood 124:771-779, 2014

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Polycythemia Vera: An Appraisal of the Biology and Management 10 Years After the Discovery of *JAK2 V617F*

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Brady L. Stein
Consulting or Advisory Role: Incyte, Sanofi Oncology
Speakers' Bureau: Incyte

Stephen T. Oh
Consulting or Advisory Role: Incyte, Gilead, CTI Biopharma, Pfizer
Speakers' Bureau: Incyte
Research Funding: Incyte (Inst), Gilead (Inst), CTI Biopharma (Inst)

Dmitriy Berenzon
Consulting or Advisory Role: Incyte

Gabriela Hobbs
No relationship to disclose

Marina Kremyanskaya
Research Funding: Incyte

Raajit Rampal
Consulting or Advisory Role: Incyte

Camille N. Abboud
Honoraria: Teva, ARIAD
Consulting or Advisory Role: Gerson Lehrman Group
Speakers' Bureau: Teva
Research Funding: Pfizer (Inst), Merck (Inst), Novartis (Inst), Sanofi/Genzyme (Inst), CTI Biopharma (Inst), Cellerant Therapeutics (Inst)

Kenneth Adler
No relationship to disclose

Mark Heaney
Consulting or Advisory Role: Blueprint, Incyte, Novartis

Elias Jabbour
No relationship to disclose

Rami Komrokji
Consulting or Advisory Role: Incyte, Celgene
Speakers' Bureau: Incyte, Celgene
Research Funding: Incyte (Inst), Celgene (Inst)
Travel, Accommodations, Expenses: Incyte, Celgene

Alison R. Moliterno
Honoraria: Incyte
Consulting or Advisory Role: Incyte

Ellen K. Ritchie
Consulting or Advisory Role: Incyte
Speakers' Bureau: Celgene, Incyte
Travel, Accommodations, Expenses: Celegene

Lawrence Rice
Consulting or Advisory Role: Amgen, Achillion, Apellis, Alexion, Synergy, Sideromics
Speakers' Bureau: Novartis, Amgen

John Mascarenhas
No relationship to disclose

Ronald Hoffman
Research Funding: Geron, Incyte, Novartis, Roche